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Seminal Plasma effectiveness in IVF treatment: Systematic review

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ABSTRACT

Background: Seminal plasma (SP) serves as a medium of transportation for sperm and a conduit for communication between the female and male reproductive organs. Preparing the female's reproductive systems for an ideal pregnancy is also one of its roles. This research aimed to investigate and gather information about the use of SP to improve cycle outcomes in IVF or ICSI. *Method:* we conducted a literate search through MEDLINE, EMBASE, PubMed, and the Cochrane Library. The results of IVF treatments for patients exposed to SP close to the time of embryo transfer or oocyte pickup were compared with those of placebo or who were not exposed to seminal plasma controls in all randomized controlled trials included in this analysis. *Results:* seven articles were included in this review with a total of 2204 participants satisfied the review's selection criteria. Two studies compared sexual activity with abstinence, the other five compared the application of SP with no intervention or with a placebo. Patients who had previously failed an IVF cycle were included in five studies. Patients with different potential reasons for implant failure were included in one study. Patients undergoing new IVF cycles with different treatment combinations included in all seven trials. The IVF features reported in all investigations were almost identical. *Conclusion:* When women are exposed to SP at the time of embryo transfer or ovum pick-up, the results are noticeably better.

Keywords: In vitro fertilization, seminal plasma, effectiveness

1. INTRODUCTION

Male accessory sex glands create a composite fluid known as seminal plasma (SP). Sperm and SP work together to accomplish a number of crucial roles related to fertilization, many of which are still poorly understood. Seminal plasma and its protein content are crucial for intravaginal transport, oviductal reservoir development, acrosome response, gamete contacts, and maintaining sperm until the appropriate moment, even though sperm contain genetic material and bind to oocytes (Pang et al., 2011). The seminal plasma that is deposited in the cervix following coitus causes significant alterations in the cell composition of the

female reproductive tract (FRT). The recruitment of immune cells to the exposed location and the release of pro-inflammatory cytokines, such as granulocyte-macrophage colony-stimulating factor and interleukin 6, are the most acute reactions to semen deposition (Sharkey et al., 2007). Peristaltic contractions cause the semen put into the lower FRT to quickly reach the higher FRT (Barnhart et al., 2001).

When exposed to SP, both endometrial epithelial cells and endometrial stromal fibroblasts release more pro-inflammatory cytokines, including leukaemia inhibitory factor, IL-1β, TNF-α, and IL-6 (Sharkey et al., 2012). Certain cytokines, like LIF, are crucial for controlling the uterine receptivity to embryo implantation and for fostering immunological tolerance at the implantation site (Aisemberg et al., 2013). The pre-implantation phase, which starts when the embryo is produced and implantation takes place, is essential to creating a long-lasting and successful pregnancy. These peri-conceptional events are primarily regulated by immune cells and maternal cytokines (Pourakbari et al., 2020). The cytokine profile in the female reproductive tract has a significant impact on both blastocyst development and implantation competence, and immune cell populations attracted to the implantation site are a major factor in endometrial receptivity. Both innate and adaptive immune system modifications are necessary to stop semi-allogeneic conceptus rejection after implantation (Robertson, 2010).

According to current research, seminal plasma plays a crucial role in training the female reproductive tracts for the best possible pregnancy outcomes in addition to serving as a medium for sperm survival (Nederlof et al., 2017). It also serves as a channel of communication between the male and female reproductive tissues. Numerous physiological processes in various FRT compartments that aid in fertilisation, implantation, and pregnancy are triggered by immune cell recruitment and cytokine release in the FRT caused by SP. Generally, SP-induced effects on FRT include priming the mother immune system to tolerate paternal antigens and semi-allograft developing foetus; in certain species, exerting positive effects on ovary through promoting ovulation, corpus luteum formation, and progesterone production; and supporting and shaping the development and growth of pre-implantation embryos Robertson, (2010), as well as promoting uterine receptivity by inducing the expression of embryo attachment molecules and angiogenic factors. The purpose of this study was to thoroughly examine and compile the data about the use of SP to enhance cycle results in women undergoing IVF or ICSI. Up to 2022, this study looked through electronic databases including MEDLINE, EMBASE, PubMed, and the Cochrane Library.

2. METHOD

We only took into consideration randomised controlled studies that used SP exposure to improve cycle outcomes during ICSI or IVF. The research participants were women of reproductive age undergoing ICSI or IVF, irrespective of the reason for their infertility. The intervention of SP exposure can be administered via intravaginal, intrauterine or intracervical injection prior to embryo replacement. Clinical pregnancy rate was regarded as the main outcome measures were as well as the live birth in the index IVF cycle. A combination of MeSH terms and key words was used to find studies involving seminal plasma (seminal fluid, seminal plasma, sexual intercourse, in-vitro fertilisation, assisted reproductive techniques, pregnancy, intracytoplasmic sperm injection, implantation, live birth, and embryo transfer). Among the limitations were human randomised control trials, but no language limit was imposed on any search.

A manual search was carried out through the list of references from the articles collected by the electronic search in order to locate cited papers that were missed by the electronic searches. The writers thoroughly reviewed the abstracts and titles of the found papers. The ones that were blatantly superfluous were removed. Before selecting which articles to include, the authors individually assessed the full texts articles. Based on internal validity elements of research design, methodological quality was assessed by authors separately; we looked for specifics on allocation concealment, randomization, intention-to-treat analysis, blinding, and follow-up. The study's baseline characteristics (aetiology, age, mean number of ET, duration of infertility), the intervention's nature (method of seminal plasma exposure, timing of seminal plasma exposure), the characteristics of the control group (placebo or no treatment), and IVF treatment cycle elements were taken from each individual study. The original articles' authors were contacted as needed to get any missing information.

3. RESULT

Initially we collected 45 articles from the electronic databases, of which 5 were removed after duplication check, the remaining 40 articles were assessed for abstract and title, 14 were removed and the remaining twenty-six full text manuscripts were examined. Of these, nineteen were discarded due to their noncompliance with the study's eligibility requirements. Consequently, seven articles with a total of 2204 participants satisfied the review's selection criteria. The description of the literature search and selection process is given in (Figure 1). All selected studies were published in full texts, randomized control trials: two compared sexual activity with abstinence, and five compared the application of SP with no intervention or with a placebo, one was a multi-center trial carried out in Spain and Australia, the other six studies were single-center investigations carried out in Australia, Middle East and Europe. Table 1 presents the characteristics of the seven research, while Table 2 lists each study's main results.

In all studies, the average age of the female research volunteers was less than 35 years. Three studies out of the seven examined infertility duration. Five studies included patients who had previously failed an IVF cycle. In just one study, patients with alternate possible causes of implantation failure were excluded. All seven trials involved patients having fresh IVF cycles with various combinations of treatments. All seven studies also reported similar IVF characteristics, such as the kind of fertilization, the number of embryos transplanted, and the stimulation approach used. Of the studies three performed an a priori power calculation and only one study successfully fulfil the anticipated sample size. Post hoc power was computed in two more experiments, often known as pilot studies.

All seven investigations reported the SP exposure procedure, albeit it varied greatly. Women who were randomized to the study group in two trials experienced their partners' SP through scheduled sexual activity around the time of ET. Using untreated semen 36–48 hours before embryo transfer, depositing prepared SP in the vagina immediately after OPU, combining intra-cervical and intra-vaginal insemination of prepared SP immediately after OPU, and intrauterine insemination of diluted SP were the intervention methods used in the remaining five studies.

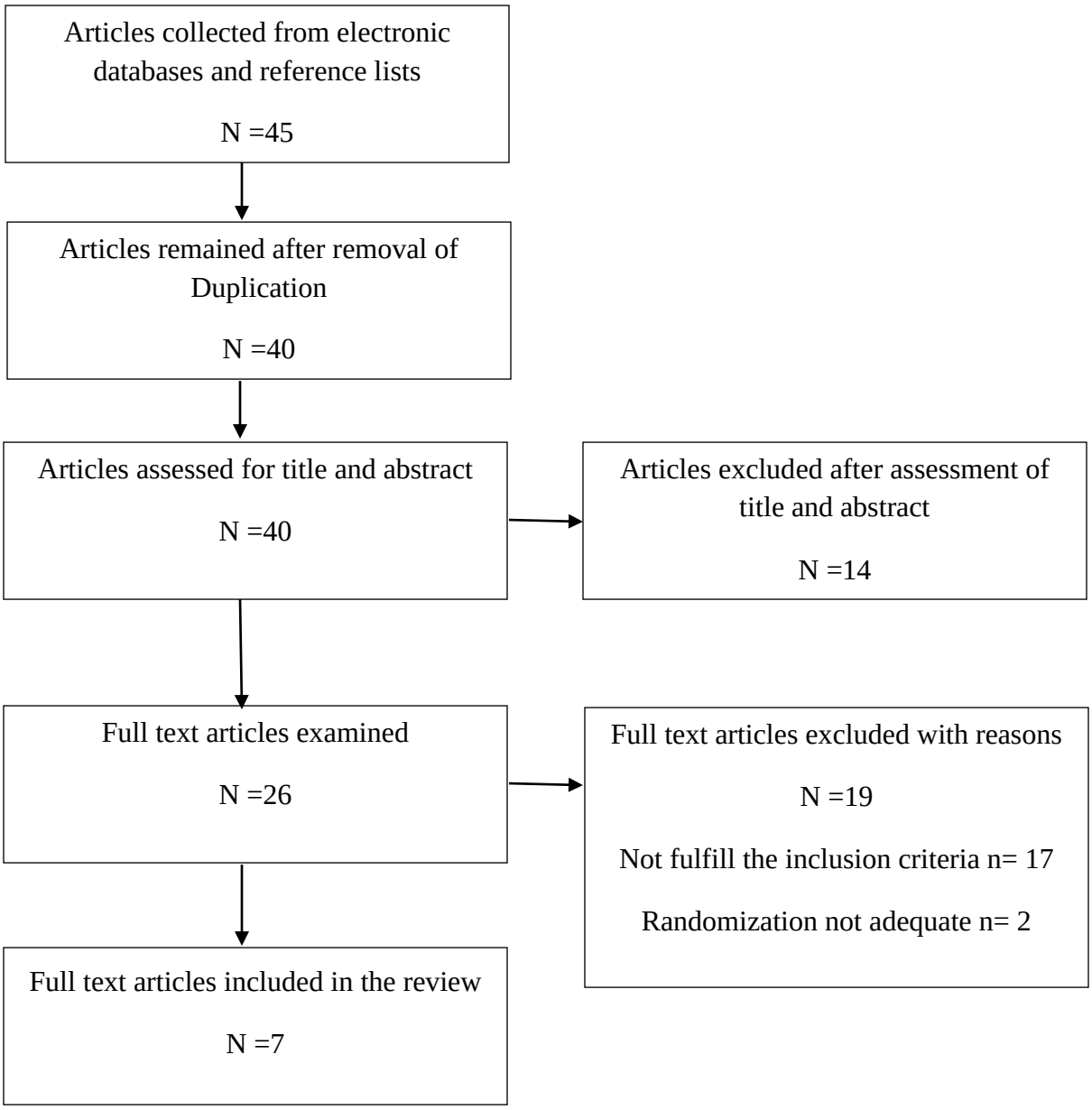

Figure 1 Consort chart of selection process

Table 1 Characteristics of included studies

Citation	Inclusion criteria	Number of participants	Control group	intervention group	Measurement of outcome	Mean age
Aflatoonian et al., 2009	Couples with infertility for more than 5 years undergoing ICSI or IVF no certain infertility	390 Divided equally into study group, and control group	Abstinence	At least one-time sexual intercourse 12 h following ET	CPR, IR	Control group: 29.5 Study group: 29.4

	cause was considered.					
Bellinge et al., 1986	Couples use fresh semen from partner for IVF, no certain infertility cause was considered	152 (74 control group, 78 study group)	No insemination or placebo	Insemination of untreated semen (0.5 to 6.0) ml 36 to 48 h before ET	CPR, IR	Control group: 31.9 Study group: 32.2
Chicea et al., 2013	Couples with previous (0 to 3) IVF trials undergoing IVF, and female age less than 38 years.	385 (200 control group, 185 study group)	No insemination or placebo	Prepared seminal plasma (0.5 ml) inseminated in cervical canal (1 to 2 cm)	CPR, IR	Controls: 33.9 Study group: 33.1
Friedler et al., 2013	Couples failed to get pregnancy after at 1 or more trials of IVF, who undergoing ICSI or IVF with female age less than 41 years	230 (124 control group, 106 study group)	0.5 ml Placebo controlled culture medium injected in the vaginal vault following	Seminal plasma (0.5) ml injected into the vaginal vault following oocyte pick-up	CPR, OPR, IR	Controls: 31.2 Study group: 32
Tremellen et al., 2000	Centre 1: couples transferring thawed embryos Centre 2: Couples getting fresh embryos transferred Female, between the ages of 18 and 40	Centre 1: total 200 (102 study group, 98 control group) Centre 2: total 400 (200 study group, 200 control group)	Abstinence	Centre 1: Having sex at least once in the two days leading up to and following ET Centre 2: At least two sexual encounters, one within 12 hours after OPU and one	IR, CPR	Centre 1 Controls: 33.1 Study group: 33.8 Centre 2 Controls: 33.2 Study group: 33.3

				within 12 hours of ET.		
Von Wolff et al., 2009	couples in a committed relationship who are having ICSI or IVF	Total 168 (control group 84, study group84)	Placebo controlled: following OPU, 0.5 ml of sodium chloride was injected into the cervical canal and the remaining 1 ml was placed in the vagina.	Following OPU, 0.5 ml of frozen seminal plasma was inseminated 2-3 cm into the cervical canal, with any leftover fluid (up to 1 ml) being placed in the vagina.	CPR	Control group: 34.1 Study group: 34.4
Von Wolff et al., 2013	Couples undergoing ICSI or IVF	Total 279 (141 control group, 138 study group)	After OPU, a 1.5 ml injection of frozen sodium chloride was administered as a placebo.	After OPU, 1.5 cc of frozen, diluted seminal plasma (ratio 1:4 with sodium chloride) was injected just above the cervix.	CPR, LBR	Control group: 34.9 Study group: 34.6

Table 2 Main findings of included studies

Citation	Main findings
Aflatoonian et al., 2009	Compared to the control group's 5.5% implantation rate, the study group's rate was 6.5%. When comparing the research patients' clinical pregnancy rates (14.2% and 11.7%, respectively) to those of the control group, there was no discernible increase. In summary the findings demonstrated that having sex during the peritransfer phase cannot improve the likelihood of becoming pregnant.
Bellinge et al., 1986	According to the data, 53% of inseminated patients had an implantation rate, as shown by an increase in human chorionic gonadotropin levels, compared to 23% in the control group. The implantation rate in the group with tubal occlusion or no fallopian tubes was 54%, and it did not differ significantly from the implantation rate in the group with patent tubes, which indicates that the endometrium was the site of sperm influence and that fallopian tube absence did not significantly affect this influence.
Chicea et al., 2013	The pregnancy rate increased in the group received SP, although not statistically significantly, and the implantation rate increased, but statistically significantly.
Friedler et al., 2013	In comparison to controls, patients who received SP intravaginal insemination

	following oocyte pick-up saw greater rates of implantation and clinical pregnancy after ET, however the difference did not achieve statistical significance. Variable methodology and additional research may provide light on SP's possible clinical benefit in raising live birth rates following ART.
Tremellen et al., 2000	The percentage of ET that were viable at 6 to 8 weeks was much greater in women who exposed to semen than in those who abstained, but there was no statistically significant difference in the pregnancy rate between the groups that engaged in sexual activity and those that did not.
Von Wolff et al., 2009	The pregnancy rate was 25.7% In placebo group. In the seminal plasma group, the clinical-pregnancy rate was 37.3%, indicating 45% relative increase.
Von Wolff et al., 2013	In the group received SP, the rate of pregnancy per randomized patient was 26.7 %, while in placebo group it was 29%. The group received SP, the live birth rate per randomised patient was 20.3%, while in placebo group, it was 23.4%.
SP; seminal plasma, ART; assisted reproductive Technology, ET; Embryo Transfer	

4. DISCUSSION

It is becoming evident that a woman's responsiveness to the implantation of an embryo and the speed at which she becomes pregnant are determined by the way her reproductive tract responds to seminal fluid. The notion that seminal plasma can improve outcomes for individuals undergoing in vitro fertilisation is not new. Even though a lot of research has been done on recently, there was little information available from these studies about the response in humans. Recent human research indicates that similar mechanisms may be implicated, which suggests that seminal fluid may not have been used to its full potential in predicting women's fertility and, more specifically, the success of IVF procedures. As far as we are aware, this systematic review is one of the few studies to gather the findings from every relevant human study that has been carried out to far. Based on the seven articles included in our study, findings indicate a considerable improvement in the pregnancy success rate following IVF therapy when seminal plasma is integrated as an additional treatment at the time of ET or OPU.

Using our data, the percentage of live births or continuing pregnancies did not considerably increase. The findings of the study force us to reconsider the advice that is typically given to IVF couples opposing abstinence. Couples undergoing IVF therapy were advised to avoid sexual activity. According to WHO there is evidence of enhanced sperm count and semen volume after one week of abstinence, which might be substantial. Some practitioners also express concerns over the possibility of multiple pregnancies, although this is uncommon if sufficient retrieval of oocyte has been performed in the infertile people undergoing IVF. More than only providing a framework for sperm survival and entry into female reproductive systems, seminal plasma exposure has other functions. Through interactions with the female reproductive organs and the accompanying inflammatory cascade, seminal plasma changes the maternal immune system to assist the development and implantation of developing embryos and create tolerance to semi-allogenic antigens.

Seminal plasma exposure during coitus triggers an immunological response that affects the progeny's number, quality, survival, and long-term health (Ahmadi et al., 2022). Leukocyte recruitment and regulatory T cell generation are stimulated by seminal fluid. By lowering inflammation, promoting uterine vascular adaptation, and preserving tolerance to foetal antigens, these cells help in embryo implantation (Robertson and Sharkey, 2016). The cytokine milieu during male seminal fluid antigen priming appears to influence the phenotype of responding T lymphocytes as well as the foetus's survival in later gestation, according to current study (Robertson et al., 2009). Personalised suggestions and consideration of a slightly greater risk of infection could also be essential. Last but not least, there is concern that the prostaglandins in seminal plasma might induce uterine contractions, perhaps making the uterine environment less suitable for the transplanted embryo.

5. CONCLUSION

The use of seminal plasma may help enhance clinical results for those undergoing IVF therapy. However, a great deal of study has to be conducted to discover the best delivery technique, timing, and influence on live birth before this additional therapy is recommended and used.

Ethical approval
Not applicable

Abbreviation list
FRT: Female reproductive tract
SP: Seminal plasma
TNF: Tumor necrosis factor
IL: Interleukin
LIF: Leukemia inhibitory factor
IVF: In vitro fertilization
ICSI: Intracytoplasmic sperm injection

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Conflict of interest
The authors declare that there is no conflict of interests.

Data and materials availability
All data sets collected during this study are available upon reasonable request from the corresponding author.

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